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<b>(21) International Application Number:</b> PCT/HU91/00014 <b>(22) International Filing Date:</b> 3 April 1991 (03.04.91)  <b>(30) Priority data:</b> 2060/90 3 April 1990 (03.04.90) HU  <b>(71)(72) Applicants and Inventors:</b> ANGELI, Tamás, Sr. [HU/HU]; Móricz Zsigmond u. 4, H-6300 Kalocsa (HU). ANGELI, Tamás, Jr. [HU/HU]; Malom u. 17, H-6300 Kalocsa (HU).  <b>(74) Agent:</b> S.B.G. AND K. PATENT AND LAW OFFICE; Dalszinház u. 10, H-1061 Budapest (HU).		<b>(81) Designated States:</b> AT (European patent), AU, BE (European patent), BG, CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FI, FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, KR, LU (European patent), NL (European patent), NO, PL, RO, SE (European patent), SU, US.  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> THERAPEUTICAL COMPOSITION AGAINST PSORIASIS ON MEDICINAL HERB BASIS  <b>(57) Abstract</b>  The present invention relates to therapeutical compositions on medicinal herb basis for the treatment of psoriasis. Another object of the invention is the preparation of the said compositions. A further object of the invention is a cosmetic composition containing the same medicinal herbs. The therapeutical composition is characterized by comprising as active ingredient the organic solvent extract of the following medicinal herbs: 4 to 20 parts by weight of celandine, 4 to 20 parts by weight of St. John's wort, 0 to 4 parts by weight of achillea, 0 to 15 parts by weight of burweed, 0 to 8 parts by weight of marigold and 0 to 6 parts by weight of camomile.  <b>BEST AVAILABLE COPY</b>		

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THERAPEUTICAL COMPOSITION AGAINST PSORIASIS ON MEDICINAL HERB  
BASIS

Technical field

The present invention relates to therapeutical compositions on medicinal herb basis for the treatment of psoriasis. Another object of the invention is the preparation of the said compositions. A further object of the invention is a cosmetic composition containing the same medicinal herbs.

Background art

10 Psoriasis constitutes one of the most common chronic skin diseases. It is a genetically determined, frequently hereditary skin disease, which appears mostly in the age of 20 to 30, and accompanies the patient through the whole life. Accordingly, only the symptoms thereof can be eliminated  
15 mostly for a certain period only, but curing is not possible yet.

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Characteristic symptoms of the disease include enhanced hornification, erythema and infiltration. Internally, the disease may be associated with articular symptoms known as arthropathea psoriatica.

5           The pathogenesis includes two important features:

- epidermopoesis enhanced to multiple of the normal as well as the morphological and biochemical modifications associated therewith. Epidermopoesis is 7 to 8-fold of the normal value. The "turn over" period of the intact epithelium  
10 is 27 days while the same is 3 to 4 days in case of psoriasis;
- the pathologically enhanced epidermopoesis can be induced with impulses on clinically intact skin of psoriatic patients (Köbner-sign).

A large number of compositions are used for external  
15 treatment of psoriasis. These are used in case of mild and medium grave indications. The grave and complicated cases need internal treatment as well. For internal treatment especially cytostatica (e.g. Methothrexat) and aromatic retinoids (Tigazon) are used. Both compositions are of strong  
20 effect, which may, however, associated with serious, sometimes even perilous side effects. Accordingly, the administration may be effected under strict medical control only.

In the external therapy, salicyl is widely used in a concentration of 5 to 10 %, in vaseline base. Salicyl dis-  
25 solves squamae rapidly, but has a minimal influence on erythema infiltrations. Accordingly, the combination thereof

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with steroids proved to be more effective. These combination contain generally 3 to 5 % of salicyl and usually fluorinated steroid. These compositions are mostly magistral but also commercial products are available, e.g. Loriden A. Preferred  
5 salicyl-steroid combination against psoriasis are the Diprosalis paint and ointment compositions. These are of very strong effect; the salicyl dissolves squamæ while the steroid component suppresses the erythema and infiltration. However, strong steroids when using on a large body surface  
10 and for a long period tend to be absorbed (which is especially characteristic in case of psoriasis) and might cause adrenocortical depression. Steroids also predispose to bacterial and fungal superinfection and may cause dermatophia and haemorrhage. The effect thereof is only temporary and in most  
15 of the cases a ready recidiva takes place.

Tar ointments have the disadvantage that only a part of the body surface is recommended to be treated as absorption from larger surface might damage the kidneys. Also patients do not like these compositions as they contaminate clothes. A  
20 combination with steroids is Loriden Tar. Tar may cause serious inflammations, and use on hairy skin is not advisable due to the danger of folliculitis.

The composition Psoriazin could not fulfil the requirements. This ointment contains mustard gas, in a dilution of 1  
25 : 20,000. Mustard gas is strongly irritative and only a few patients can tolerate.

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Ditranol has been used in the treatment of psoriasis for long. In a more dilute form (1 - 5 %) the ointment caused a slow, continuous improvement, however, nowadays the so-called "flush" treatment with a more concentrated composition is more preferred, wherein the daily treatment takes 1 to 1 hour followed by careful removal of the rests. The composition is highly effective, but very drastic; it induces serious inflammations and accordingly, treatment may be performed only under clinical conditions, home treatment should be avoided.

PUVA and SUVA treatment is also used in case of psoriasis. The apparatus emits selective PUVA, the so-called "black light". In the PUVA treatment photosensibilisator is also added, or possibly 6-methoxy-psoralen is applied by painting. The apparatus is, however, very difficult to obtain and very expensive. The scope of contraindications is very broad and accordingly, the number of possible treatments is limited.

The Psoricur oil is based on the oily extract of different medicinal herbs, among others *Allium sativum* (garlic). This composition is described in the specification PCT/HU87/00060 published under WO89/05651. Recent experiments showed that the treatment induced frequently serious inflammations. On the other hand, the treatment is quite expensive.

In our Hungarian Patent No. 196,557 a composition comprising organic solvent extract of medicinal herbs in natural carrier is described. The composition is a brownish-

green ointment which is easy to smear and is well-penetrating. Application is suitably made in the evening by rubbing in the skin several times. The composition possesses sufficient therapeutical activity, within a few days squama formation ceases and erythema and infiltration decreases, first in the center of the plaque, while the peripheral ring disappears at last. Symptom-free state was observed after 5 to 6 months, in some cases 2 to 3 months. As the said composition consists of natural materials only, use on even the entire body surface is also possible, and home treatment is also possible considering that no specific external side-effects were observed, like inflammation, folliculitis, fungal, bacterial complications, etc.

However, also this composition possesses some drawbacks, e.g. the effect is too slow, and the use thereof may be hazardous to health as one of the components, i.e. birthwort (*Aristolochia folium*) is toxic and regarded as carcinogenic, and accordingly, use thereof is also prohibited in different countries.

Accordingly, the present invention aims to provide a composition which serves for a permanent suppression of psoriasis, possesses no toxicity, can be used in the home practice without limitations, even more times a day and the effect appears within a short treatment period; the effect is prolonged and no symptoms reappear on the recovered skin surface.

Disclosure of the invention

The present invention provides a composition against psoriasis which comprises the extract of a combination of the medicinal herbs celandine and St. John's wort as well as  
5 optionally achillea, burweed, marigold and camomile as active ingredient. The composition preferably contains at least one dermatologically acceptable pharmaceutical or cosmetical additive.

The book Rápóti, J., Romvári, V.: Medicinal plants  
10 (1975) provides the following information about the above plants:

## 1. Burweed:

The drug (Bardanae radix) contains a small amount of volatile oils, tannic material, resin, sterins, 20 to 50 % of  
15 inulin, mucin, fats, sugar, organic acids as well as bitter materials. The decoction per se or tea blend is used as diuretic, biliary and renal calculus litholytic, blood purifying, choleretic agent. Externally, the decoction is used against herpes, eczema, impetigo, as rinsing, against pharyn-  
20 gitis as gargle. As hair care cosmetical agent may also be used.



## 2. Celandine:

The drug (*Chelodini herba*) and root (*Cheladonii radix*) have a bitter, irritating taste, the powder thereof, when inhaling, stimulates coughing and sneezing. The drug contains  
5 several alkaloids, resins, volatile oils, vitamin C, nicotinic acid, etc. The active material content of the root is richer than that of the drug. Both drugs are used for preparing medicines against bilious and liver disorders in large scale. The drugs per se cannot be used for preparing tea;  
10 also the use thereof in tea blends should be confirmed by physician. The juice of fresh plant is used to eliminate corn and wart.

## 3. Camomile:

The drug (*Chamomile flos*) contains 0.2 to 0.7 % of dark  
15 blue volatile oil with a sulene content of 3 to 5%, as well as glucosides, tannic material, bitter components, vegetable acids and sugar.

The camomile flower is one of the most commonly known and used domestic medicines, also registered in the pharmacopeiae of most countries. The decoction thereof possesses  
20 the following effects: tranquillizing, spasmolytic, carminative, stomachic, digestive, diaphoretic, disinfectant, gastrointestinal disease curing effects. Externally, it is used

as eye pack, throat gargle and gingival recuperative agent. It can be used not only as medicinal tea but also as regular drink due to the pleasant taste thereof.

4. Marigold:

5           The drug (*Calendula flos sine calicibus*) contains carotene, glucosides, bitter components, small amount of volatile oil and color materials. The decoction is used against gastric and intestinal ulcer externally, as well as for packing slowly healing wounds and ulcer. The colouring  
10 component thereof is used for colouring food, medicines and drinks.

5. St. John's wort:

          The drug (*Hyperici herba*) contains glucosides, tannic material, colouring agents, sugar, choline, pectin, nicotinic  
15 acid, etc. The tea is used against gastric and intestinal ulcer, hypertension, digestive troubles, internal and external bleedings, renal and bilious diseases. Externally, the decoction is used in the treatment of slight skin disorders and slowly healing wounds. As rinsing agent, it is recommend-  
20 ed against pharyngitis and paradentosis.

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## 6. Achillea:

The drug (Millefolii herba) contains an azulene-containing, blue volatile oil in an amount of 0.1 to 1.5% as well as the glucoalkaloid achillein, bitter components, tannic material, conitic acid, aspargene, glycoside, fatty oil, resin, carbohydrate. The achillea oil is the active component of anti-inflammatory ointments, e.g. for the treatment of eyes, as well as in facial creams and skin-care compositions. The azulene ointment does not suppress inflammation, but accelerates the process. The drugs and teas of achille are used as appetizers, digestives, spasmolitica, for promoting bile- and liver functions, eliminating menstrual disorders, curing urinary and respiratory disorders and hypertension. The indication also includes the treatment of varicosity, enteritis and gastroenteritis, as well as prostatic disorders. Externally, the decoction serves as gargle and pack against gingival, eye, and general inflammations.

The active material of the composition according to the present invention is the extract of the following components:

20	celandine	4 to 16 parts by weight
	St. John's wort	4 to 20 parts by weight
	achillea	0 to 4 parts by weight
	burweed	0 to 15 parts by weight
	marigold	0 to 8 parts by weight
25	camomile	0 to 6 parts by weight.

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Especially preferred are the compositions of the present invention which contain achillea as a compulsory component.

The medicinal herb extract used as the active component  
5 of the composition of the present invention is obtained by organic solvent extraction. As organic solvent, preferably a polar solvent, e.g. ethyl acetate, an alcohol or acetone is used. Especially preferred is the use of acetone.

The carrier of the composition may be any pharmaceutical  
10 cal or cosmetic carrier which can be used on the skin. The compositions are suitably in the form of cream, ointment or oily elixir. As carrier for the preparation of the present compositions suitably linseed oil, cholesterol, vaseline, Adeps lanae and distilled water can be used. Preferred carriers  
15 are the linseed oil and cholesterol.

The ratio of the active material - i.e. the medicinal herb extract - and the carrier is not a critical factor and may vary between broad ranges. It is important, however, that the carrier must be present in an amount sufficient to retain  
20 the composition on the surface, and to ensure penetration through the skin.

The compositions according to the invention can be prepared e.g. by milling the above dry herbs, followed by extracting suitably each separately in a suitable amount of  
25 polar organic solvent at a temperature not exceeding 60°C, filtering the mixtures, combining the filtrates, followed by

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evaporating to dry. After evaporation, the active ingredients are dissolved in a solvent which is not skin irritative, e.g. ethanol, and incorporated as a solution in the suitable carrier(s). Under continuous stirring, the composition is  
5 filled into tubes, jars and flasks, resp., sealed and stored in dry, cool conditions.

According to a preferred embodiment of the invention, the mixture of cholestrol, Vaselinum album, Cera lanæ, Oleum lini and Aqua destillatum are used to formulate a cream. A  
10 composition for use on psoriasis of hairy scalp can be obtained preferably by using Oleum lini containing suitably 0.01 % of  $\alpha$ -d,l-tocopherol, i.e. vitamin E, as natural antioxidant. The oil composition is filled into flasks or flacons.

15 Application of the compositions is accomplished by smearing the skin surface several times daily or only once but for a longer period, e.g. 2 to 3 hours. Treatment of psoriatic skin surface results in ceasing of squama formation within one week. During this period the characteristic ten  
20 sive, burning and itching feeling disappears or substantially decreases. Subsequently, also erythema and infiltration tend to disappear, first in the plaque center and finally, only a peripheral ring remains.

The continuous pachydermia, the most painful form of  
25 which appears on palm and sole, needs a longer treatment, i.e., even by a daily treatment of 2 to 3 hours recovery

needs a longer period. However, even in these cases a rapid and substantial recovery will be observed, pain is strongly subsided, tension, haemorrhage and clefts slowly disappear. In the first period, only the number thereof decreases rapidly, then the pathologically thick skin begins to desquamate, erythema is formed on large area in place of the squamae, followed by intensive disappearance thereof, and thus, a normal epidermis is gradually forming. The limbs, in contrary to the previous state, can be used properly. The regeneration of skin of youngers and those having browner skin needs generally less time.

In certain cases, following a longer treatment period, reappearance of the characteristic symptoms was observed, however, a short treatment resulted in a very quick recovery.

Surprisingly it has been found that the compositions of the present invention can be used not only in the treatment of psoriasis but also on other pathological dermatitis. Thus, rubors, desquamation and induration of the skin can also be prevented by using the compositions. Esthetical appearance of the skin having been treated and regularly cared improved substantially. Accordingly, the present compositions may be used also as cosmetics.

The compositions of the present invention have the advantage that they consist of natural ingredients exclusively, which are unharmed to the human organism, possessing at the same time disinfecting and skin nutritioning effect. This

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effect meets recent tendencies which prefers natural pharmaceutical products and cosmetics to synthetic compositions. Their use is very simple and can be applied on the same surface several times daily.

- 5           A most preferred application form is the use for treating psoriasis of hairy scalp in the form of an oily composition, which treatment was very difficult in the past.

The following examples serve for illustrating the present invention more in details:

10   Best mode of carrying out the invention

Example 1

Extract of medicinal herbs was prepared from the following dry plants:

	burweed	120 g
15	celandine	100 g
	St.John's wort	100 g
	marigold	60 g
	camomile	50 g
	achillea	40 g

- 20           Each of the above plants were separately milled into powder, extracted in a suitably apparatus with acetone at a temperature not exceeding 60°C, the extracts were filtered, combined and evaporated at a temperature not exceeding 60°C,

followed by cooling to room temperature. The extract thus obtained was dissolved in 96,3% ethanol at about 50°C and used in the preparation of 5,000 g pharmaceutical composition.

5    Example 2

The medicinal herb extract obtained in Example 1 was formulated into pharmaceutical composition as follows:

250 g of Cholesterinum, 1,500 g of Vaselinum album, 1,500 g of Cera lanæ, 1,600 g of oleum linii and the extract  
10 obtained in Example 1 (filled up to 150 g with Aqua dest.) were homogenized by stirring and filled into tubes under continuous stirring at 45 to 50°C. The brownish-green cream thus obtained was stored in cool place.

Example 3

15        For preparing a composition especially for treating psoriasis of hairy scalp the extract of Example 1 was diluted with Aqua dest. and stirred into 5000 g of Oleum linii containing 0.01 % vitamin E under continuous stirring, the composition was filled into suitable flasks.



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## Example 4

Treatments were carried out with the composition of Example 1 on a total of 92 patients. Treatment was performed once a day in the evening. After showering, the patients were treated by rubbing the composition in the skin, while one hour later the non-absorbed ointment rests were removed. The control group consisted of 60 patients, treated with 5% salicylic acid or fluorinated steroid. The treatments were carried out in a period of 3 months.

The results of therapy are summarized as herebelow:

	Symptom-free:	35%
	Substantial improvement:	40%
	Moderate improvement:	11%
	No change:	13%
15	Worsening:	1%

Summarized, the effect of the composition was much better than that of the control group. No side effects, except for the one case, were observed.

The photosensibilizing and skin irritating effect of the composition of example 2 was tested on albino guinea pigs. During 3 months treatment negative results were obtained in both effects.

Claims

1. Therapeutical composition against psoriasis characterized by comprising as active ingredient the organic solvent extract of the following medicinal herbs: 4 to 20 parts  
5 by weight of celandine, 4 to 20 parts by weight of St. John's wort, 0 to 4 parts by weight of achillea, 0 to 15 parts by weight of burweed, 0 to 8 parts by weight of marigold and 0 to 6 parts by weight of camomile.
2. Cosmetic composition against psoriasis characterized  
10 by comprising as active ingredient the organic solvent extract of the following medicinal herbs: 4 to 20 parts by weight of celandine, 4 to 20 parts by weight of St. John's wort, 0 to 4 parts by weight of achillea, 0 to 15 parts by weight of burweed, 0 to 8 parts by weight of marigold and 0  
15 to 6 parts by weight of camomile.
3. The composition according to claim 1 characterized in that the extract is a polar organic solvent extract.
4. The composition according to claim 1 characterized in that the extract is an acetone extract.
- 20 5. The composition according to claim 1 characterized by comprising at least one pharmaceutically acceptable carrier.

6. The composition according to claim 5 characterized in that the carrier is linseed oil.

7. The composition according to claim 5 characterized in that the carrier is cholesterol, vaseline, Adeps lanae,  
5 linseed oil and distilled water.

8. The composition according to claim 1 characterized in that 1,25 kg composition contains the extract of 30 g burweed, 25 g celandine, 25 g St.John's wort, 15 g marigold, 12,5 g camomile and 10,9 g achillea.

10 9. The composition of claim 8 characterized in that as carrier, one kg composition contains 62,5 g cholesterol, 37,5 g vaseline, 375 g Adeps lanae, 400 g linseed oil and 37,5 g distilled water.

10. Process for preparing therapeutical composition  
15 against psoriasis characterized in that 4 to 20 parts by weight of celandine, 4 to 20 parts by weight of St.John's wort, 0 to 4 parts by weight of achillea, 0 to 15 parts by weight of burweed, 0 to 8 parts by weight of marigold and 0 to 6 parts by weight of camomile are extracted with an organ-  
20 ic solvent, and the extract thus obtained is formulated with at least one pharmaceutically acceptable carrier.

# INTERNATIONAL SEARCH REPORT

International Application No. PCT/HU 91/00014

<b>I. CLASSIFICATION OF SUBJECT MATTER</b> (if several classification symbols apply, indicate all) <sup>6</sup> According to International Patent Classification (IPC) or to both National Classification and IPC <div style="margin-top: 10px;">Int. Cl.<sup>5</sup>: A 61 K 35/78</div>											
<b>II. FIELDS SEARCHED</b> <div style="text-align: right; margin-right: 100px;">Minimum Documentation Searched <sup>7</sup></div> <table style="width: 100%; border: none;"> <tr> <td style="width: 50%; border: none;">Classification System</td> <td style="width: 50%; border: none;">Classification Symbols</td> </tr> <tr> <td style="border: none; padding-top: 10px;">Int. Cl.<sup>5</sup>: A 61 K</td> <td style="border: none;"></td> </tr> </table> <div style="margin-top: 10px; text-align: center; font-size: small;">Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched <sup>8</sup></div>			Classification System	Classification Symbols	Int. Cl. <sup>5</sup> : A 61 K						
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Int. Cl. <sup>5</sup> : A 61 K											
<b>III. DOCUMENTS CONSIDERED TO BE RELEVANT <sup>1</sup></b> <table style="width: 100%; border: none;"> <tr> <th style="width: 10%; border: none;">Category <sup>9</sup></th> <th style="width: 70%; border: none;">Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup></th> <th style="width: 20%; border: none;">Relevant to Claim No. <sup>13</sup></th> </tr> <tr> <td style="border: none; text-align: center; vertical-align: top; padding: 10px;">Y</td> <td style="border: none; padding: 10px;">FR, A1, 2 342 071 (LABORATOIRE DE THERAPEUTIQUES PHYSIOLOGIQUES) 23 September 1977 (23.09.77), see claims.</td> <td style="border: none; text-align: center; vertical-align: top; padding: 10px;">(1)</td> </tr> <tr> <td style="border: none; text-align: center; vertical-align: top; padding: 10px;">Y</td> <td style="border: none; padding: 10px;">WO, A1, 89/05 651 (PSORICUR LTD.) 29 June 1989 (29.06.89), see claims 1,2,6,7,10.</td> <td style="border: none; text-align: center; vertical-align: top; padding: 10px;">(1,5,10)</td> </tr> </table>			Category <sup>9</sup>	Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claim No. <sup>13</sup>	Y	FR, A1, 2 342 071 (LABORATOIRE DE THERAPEUTIQUES PHYSIOLOGIQUES) 23 September 1977 (23.09.77), see claims.	(1)	Y	WO, A1, 89/05 651 (PSORICUR LTD.) 29 June 1989 (29.06.89), see claims 1,2,6,7,10.	(1,5,10)
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<div style="display: flex; justify-content: space-between; font-size: x-small;"> <div style="width: 45%;"> <p><sup>*</sup> Special categories of cited documents: <sup>10</sup></p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&amp;" document member of the same patent family</p> </div> </div>											
<b>IV. CERTIFICATION</b> <table style="width: 100%; border: none;"> <tr> <td style="width: 50%; border: none; vertical-align: top;">           Date of the Actual Completion of the International Search  <div style="margin-top: 10px;">08 May 1991 (08.05.91)</div> </td> <td style="width: 50%; border: none; vertical-align: top;">           Date of Mailing of this International Search Report  <div style="margin-top: 10px;">04 June 1991 (04.06.91)</div> </td> </tr> <tr> <td style="border: none; vertical-align: top;">           International Searching Authority  <div style="margin-top: 10px;">AUSTRIAN PATENT OFFICE)</div> </td> <td style="border: none; vertical-align: top;">           Signature of Authorized Officer  <div style="margin-top: 10px; text-align: center;"> </div> </td> </tr> </table>			Date of the Actual Completion of the International Search <div style="margin-top: 10px;">08 May 1991 (08.05.91)</div>	Date of Mailing of this International Search Report <div style="margin-top: 10px;">04 June 1991 (04.06.91)</div>	International Searching Authority <div style="margin-top: 10px;">AUSTRIAN PATENT OFFICE)</div>	Signature of Authorized Officer <div style="margin-top: 10px; text-align: center;"> </div>					
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